

CLAIMS

WHAT IS CLAIMED IS:

1. A method for treating neuropathic pain in a subject, the method comprising administering to the subject a formulation comprising a neublastin polypeptide at a dosage of between 1 $\mu\text{g/kg}$ to 30,000 $\mu\text{g/kg}$ body weight of the subject, per dose.
2. The method of claim 1 wherein the neuropathic pain is associated with post-herpetic neuralgia, diabetic neuropathy, or sciatica.
3. A method for treating tactile allodynia in a subject, the method comprising administering to the subject a neublastin polypeptide at a dosage of between 10 $\mu\text{g/kg}$ to 30,000 $\mu\text{g/kg}$ body weight of the subject per dose.
4. The method of claim 1 or 3, wherein the neublastin polypeptide is administered using a delivery system selected from the group consisting of intravenous delivery, intramuscular delivery, intrapulmonary delivery, subcutaneous delivery, and intraperitoneal delivery.
5. The method of claim 1 or 3, wherein the neublastin polypeptide is administered via intramuscular delivery or subcutaneous delivery.
6. The method of claim 1 or 3 wherein the dosage is between 10 $\mu\text{g/kg}$ to 10,000 $\mu\text{g/kg}$ body weight of the subject, per dose.
7. The method of claim 1 or 3 wherein the dosage is between 25 $\mu\text{g/kg}$ to 3,000 $\mu\text{g/kg}$ body weight of the subject, per dose.

8. The method of claim 1 or 3, wherein said the amino acid sequence of said neublastin polypeptide comprises a polypeptide selected from the group consisting of:

(a) at least one polypeptide comprising AA₈₀-AA₁₄₀ of SEQ ID NO:2, AA₄₁-AA₁₄₀ of SEQ ID NO:2, AA₁-AA₁₄₀ of SEQ ID NO:2, AA₂₅-AA₁₄₀ of SEQ ID NO:2, AA₂₈-AA₁₄₀ of SEQ ID NO:2, AA₈₀-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₂₂₄ of SEQ ID NO:5, or AA₈₁-AA₂₂₄ of SEQ ID NO:5;

(b) at least one polypeptide comprising the C-terminal sequence set forth in either AA₁₀₇-AA₁₄₀ of SEQ ID NO:2 or AA₇₆-AA₁₄₀ of SEQ ID NO:2, and which retain the seven Cys residues characteristic of the GDNF family and of the TGF- β super family;

(c) at least one polypeptide comprising SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27; and

(d) at least one polypeptide sequence that has greater than 70% amino acid homology to any one of the sequences in (a) - (c) above.

9. The method of claim 1 or 3, wherein the neublastin polypeptide is administered in a timed-release composition.

10. The method of claim 1 or 3 wherein the neublastin polypeptide is modified with a derivative moiety to have an extended residence time and/or increased concentration in body fluids.

11. The method of claim 10 wherein the derivative moiety is a polyethylene glycol moiety.

12. The method of claim 10 wherein the derivative moiety is selected from the group consisting of aliphatic esters, amides, N-acyl-derivatives, or O-acyl derivatives.

13. A method for treating neuropathic pain in a subject comprising:

- a) administering to the subject an effective amount of a neublastin polypeptide;
and
- b) administering to the subject an effective amount of an analgesia-inducing compound selected from the group consisting of opioids, anti-arrhythmics, topical analgesics, local anaesthetics, anticonvulsants, antidepressants, corticosteroids and NSAIDS.

14. The method of claim 13 wherein the neuropathic pain is associated with post-herpetic neuralgia, diabetic neuropathy, or sciatica.

15. A method for treating tactile allodynia in a subject, the method comprising:
- a) administering to the subject an effective amount of a neublastin polypeptide;
and
 - b) administering to the subject an effective amount of an analgesia-inducing compound selected from the group consisting of opioids, anti-arrhythmics, topical analgesics, local anaesthetics, anticonvulsants, antidepressants, corticosteroids and NSAIDS.

16. The method of claim 13 or 15 wherein the analgesia-inducing compound in (b) is an anticonvulsant.

17. The method of claim 13 or 15 wherein the analgesia-inducing compound in (b) is gabapentin (1-(aminomethyl)cyclohexane acetic acid) or pregabalin (S-(+)-4-amino-3-(2-methylpropyl)butanoic acid).

18. The method of claim 13 or 15, wherein the neublastin polypeptide is administered using a delivery system selected from the group consisting of intravenous delivery, intramuscular delivery, intrapulmonary delivery, subcutaneous delivery, and intraperitoneal delivery.

19. The method of claim 13 or 15, wherein the neublastin polypeptide is administered via intramuscular delivery or subcutaneous delivery.

20. The method of claim 13 or 15 wherein the dosage of the neublastin polypeptide is between 10 µg/kg to 10,000 µg/kg body weight of the subject, per dose.

21. The method of claim 13 or 15 wherein the dosage of the neublastin polypeptide is between 25 µg/kg to 3,000 µg/kg body weight of the subject, per dose.

22. The method of claim 13 or 15, wherein said the amino acid sequence of said neublastin polypeptide comprises a polypeptide selected from the group consisting of:

(a) at least one polypeptide comprising AA₈₀-AA₁₄₀ of SEQ ID NO:2, AA₄₁-AA₁₄₀ of SEQ ID NO:2, AA₁-AA₁₄₀ of SEQ ID NO:2, AA₂₅-AA₁₄₀ of SEQ ID NO:2, AA₂₈-AA₁₄₀ of SEQ ID NO:2, AA₈₀-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₂₂₄ of SEQ ID NO:5, or AA₈₁-AA₂₂₄ of SEQ ID NO:5;

(b) at least one polypeptide comprising the C-terminal sequence set forth in either AA₁₀₇-AA₁₄₀ of SEQ ID NO:2 or AA₇₆-AA₁₄₀ of SEQ ID NO:2, and which retain the seven Cys residues characteristic of the GDNF family and of the TGF-beta super family;

(c) at least one polypeptide comprising SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27; and

(d) at least one polypeptide sequence that has greater than 70% amino acid homology to the sequences in (a) - (c) above.

23. The method of claim 13 or 15, wherein the neublastin polypeptide is administered in a timed-release composition.

24. The method of claim 13 or 15 wherein the neublastin polypeptide is modified with a derivative moiety to have an extended residence time and/or increased concentration in body fluids.

25. The method of claim 24 wherein the derivative moiety is a polyethylene glycol moiety.

26. The method of claim 24 wherein the derivative moiety is selected from the group consisting of aliphatic esters, amides, N-acyl-derivatives, or O-acyl derivatives.

27. The method of claims 1 or 13, wherein said neuropathic pain is associated with infection of said subject by a virus.

28. The method of claim 27, wherein said virus is selected from the group consisting of a herpes virus, a human immunodeficiency virus (HIV), a papilloma virus.

29. The method of claims 1 or 13, wherein said neuropathic pain is neuropathic pain associated with administration of a therapeutic agent.

30. The method of claim 29, wherein said therapeutic agent is an anti-cancer agent.

31. The method of claim 30 wherein the anti-cancer agent is selected from the group consisting of taxol, taxotere, cisplatin, nocodazole, vincristine, vindesine and vinblastine.

32. The method of claim 29, wherein said therapeutic agent is an anti-viral agent.

33. The method of claim 32, wherein said anti-viral agent is selected from the group consisting of ddI, DDC, d4T, foscarnet, dapsone, metronidazole, and isoniazid.

34. The method of claim 1 or 13, wherein said neuropathic pain is due to injury associated with trauma.

35. The method of claim 1 or 13, wherein said neuropathic pain is allodynia.

36. The method of claim 1 or 13, wherein said neuropathic pain is hyperalgesic pain.

37. The method of claim 36 wherein the hyperalgesic pain is thermal hyperalgesia.

38. The method of claim 1 or 13, wherein said neuropathic pain is phantom pain.

39. The method of claim 1 or 13, wherein the neuropathic pain is associated with hereditary neuropathy (including but not limited to Friedreich ataxia, familial amyloid polyneuropathy, Tangier disease, Fabry disease), metabolic disorders (including but not limited to renal insufficiency and hypothyroidism), vitamin deficiencies (including but not limited to vitamin B12 deficiency, vitamin B6 deficiency, and vitamin E deficiency), toxic and iatrogenic neuropathies (including but not limited to alcoholism, vitamin B6 intoxication, hexacarbon intoxication, amiodarone, chloramphenicol, disulfiram, isoniazide, gold, lithium, metronidazole, misonidazole, nitrofurantoin), infectious neuropathies (including but not limited to leprosy, Lyme disease), auto-immune neuropathies (including but not limited to Guillain-Barre syndrome, chronic inflammatory de-myelinating polyneuropathy, monoclonal gammopathy of undetermined significance and polyneuropathy), trigeminal neuralgia, entrapment syndromes (including but not limited to Carpel tunnel), post-traumatic neuralgia, phantom limb pain, multiple sclerosis pain, complex regional pain syndromes (including but not limited to reflex sympathetic dystrophy, causalgia), neoplasia, vasculitic/angiopathic neuropathy and idiopathic neuropathy.

40. A method for reducing the loss of pain sensitivity in a subject afflicted with a neuropathy, the method comprising administering a formulation comprising a neublastin polypeptide at a dosage of between 1 µg/kg to 30,000 µg/kg body weight of the subject, per dose.

41. The method of claim 40 wherein the neuropathy is diabetic neuropathy.

42. The method of claim 40 wherein the loss of pain sensitivity is a loss in thermal pain sensitivity.

43. The method of claim 40, wherein the neublastin polypeptide is administered using a delivery system selected from the group consisting of intravenous delivery, intramuscular delivery, intrapulmonary delivery, subcutaneous delivery, and intraperitoneal delivery.

44. The method of claim 40, wherein the neublastin polypeptide is administered via intramuscular delivery or subcutaneous delivery.

45. The method of claim 40 wherein the dosage is between 10 µg/kg to 10,000 µg/kg body weight of the subject, per dose.

46. The method of claim 40 wherein the dosage is between 25 µg/kg to 3,000 µg/kg body weight of the subject, per dose.

47. The method of claim 40, wherein said the amino acid sequence of said neublastin polypeptide comprises a polypeptide selected from the group consisting of:

(a) at least one polypeptide comprising AA₈₀-AA₁₄₀ of SEQ ID NO:2, AA₄₁-AA₁₄₀ of SEQ ID NO:2, AA₁-AA₁₄₀ of SEQ ID NO:2, AA₂₅-AA₁₄₀ of SEQ ID NO:2, AA₂₈-AA₁₄₀ of SEQ ID NO:2, AA₈₀-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₂₂₄ of SEQ ID NO:5, or AA₈₁-AA₂₂₄ of SEQ ID NO:5;

(b) at least one polypeptide comprising the C-terminal sequence set forth in either AA₁₀₇-AA₁₄₀ of SEQ ID NO:2 or AA₇₆-AA₁₄₀ of SEQ ID NO:2, and which retain the seven Cys residues characteristic of the GDNF family and of the TGF-beta super family;

(c) at least one polypeptide comprising SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27; and

(d) at least one polypeptide sequence that has greater than 70% amino acid homology to the sequences in (a) - (c) above.

48. The method of claim 40, wherein the neublastin polypeptide is administered in a timed-release composition.

49. The method of claim 40 wherein the neublastin polypeptide is modified with a derivative moiety to have an extended residence time and/or increased concentration in body fluids.

50. The method of claim 40 wherein the derivative moiety is a polyethylene glycol moiety.

51. The method of claim 40 wherein the derivative moiety is selected from the group consisting of aliphatic esters, amides, N-acyl-derivatives, or O-acyl derivatives.

52. A method for treating, preventing or delaying neuropathic pain in a subject, the method comprising administering to the subject a formulation comprising a neublastin polypeptide at a dosage of between 1 $\mu\text{g/kg}$ to 30,000 $\mu\text{g/kg}$ body weight of the subject, per dose, wherein administering of neublastin polypeptide is prophylactic.

53. The method of claim 52, wherein the neublastin polypeptide is administered using a delivery system selected from the group consisting of: intravenous delivery, intramuscular delivery, intrapulmonary delivery, subcutaneous delivery, and intraperitoneal delivery.

54. A method for treating diabetic neuropathy in a subject, the method comprising administering to the subject a formulation comprising a neublastin polypeptide at a dosage of between 1 $\mu\text{g/kg}$ to 30,000 $\mu\text{g/kg}$ body weight of the subject, per dose.

55. The method of claim 52 or 54, wherein the neublastin polypeptide is administered using a delivery system selected from the group consisting of intravenous delivery, intramuscular delivery, intrapulmonary delivery, subcutaneous delivery, and intraperitoneal delivery.

56. The method of claim 52 or 54, wherein said the amino acid sequence of said neublastin polypeptide comprises a polypeptide selected from the group consisting of:

- (a) at least one polypeptide comprising AA₈₀-AA₁₄₀ of SEQ ID NO:2, AA₄₁-AA₁₄₀ of SEQ ID NO:2, AA₁-AA₁₄₀ of SEQ ID NO:2, AA₂₅-AA₁₄₀ of SEQ ID NO:2, AA₂₈-AA₁₄₀ of SEQ ID NO:2, AA₈₀-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₁₄₄ of SEQ ID NO:4, AA₁-AA₂₂₄ of SEQ ID NO:5, or AA₈₁-AA₂₂₄ of SEQ ID NO:5;
- (b) at least one polypeptide comprising the C-terminal sequence set forth in either AA₁₀₇-AA₁₄₀ of SEQ ID NO:2 or AA₇₆-AA₁₄₀ of SEQ ID NO:2, and which retain the seven Cys residues characteristic of the GDNF family and of the TGF- β super family;
- (c) at least one polypeptide comprising SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 or SEQ ID NO:27; and
- (d) at least one polypeptide sequence that has greater than 70% amino acid homology to any one of the sequences in (a) - (c) above.